UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

AK

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/556,038	11/09/95	BOUSSIOTIS V	RPI-022CP

HM12/0418

LAHIVE & COCKFIELD, LLP
28 STATE STREET
BOSTON MA 02109

EXAMINER	
BOARK, J	
ART UNIT	PAPER NUMBER
1644	25

DATE MAILED:
04/18/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	08/556,038	BOUSSIOTIS ET AL.	
	Examiner	Art Unit	
	Jessica H. Roark	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48,72-75,77-91,93-98 and 102* is/are pending in the application.

4a) Of the above claim(s) *10,48,72-75,77-91 and 93-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Jessica Roark, Group Art Unit 1644, Technology Center 1600.

2. Applicant's election without traverse of Group II (claim 98) in Paper No. 24 is acknowledged.

Claims 48, 72-75, 77-91, 93-97 and 102 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claim 98 is under consideration in the instant application.

3. (As noted in Paper No. 22): The request filed on 7/17/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/556,038 is acceptable and a CPA has been established. An Office Action on the CPA follows.

4. Instant claim 98 appears to have adequate written support in parent application USSN 08/270,152 (7/1/94). Therefore the priority date of instant claim 98 is considered to be 7/1/94.

5. Applicant's IDS, filed 4/5/96 (Paper No. 4), is acknowledged.

6. This Application has been filed with informal drawings which are acceptable for examination purposes only.

7. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

8. Claim 98 is objected to because of the following informalities: As set forth in Paper Nos. 17 and 22, "inhibiting responsiveness in an anergic T cell" is considered to be stimulating a response in said T cells since anergic T cells are unresponsive. Applicant is requested to provide positive claim language, such as "preventing the induction of anergy in a T cell", as supported in Examples 2-4.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 98 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the agents IL-2, IL-4, IL-7, or an antibody to the common γ chain in preventing induction of anergy *in vitro*; does not reasonably provide enablement for either the full breadth of "agent" as recited, the reversal of anergy, or the prevention or reversal of anergy *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide sufficient guidance and direction with respect to "agent" as broadly recited. The specification discloses on pages 5 and 12 that "agent" can be the cytokines IL-2, IL-4, IL-7, IL-15 (page 5); antibodies to the common γ chain (page 5); or even peptide fragments of cytokines, peptide mimetics, other small molecules, or intracellular agents (page 12).

A person of skill in the art is not enabled to make and use "agent" as encompassed by the full breadth of the claim as currently recited. For example, Applicant provides data that cross-linking antibodies can prevent the induction of anergy in an *in vitro* culture system (Example 2). However, the skilled artisan would not expect antibodies which do not cross link to mediate this effect. Furthermore, Applicant does not appear to provide enabling support for peptide fragments of cytokines, peptide mimetics, and other small molecules as either *in vitro* or *in vivo* agents for use in inhibiting responsiveness in an anergic T cell. The skilled artisan at the time the invention was made recognized that the use of fragments, mimetics, and especially small molecules to substitute for an effect observed for physiological ligands is fraught with uncertainties. Huang (Pharmacol. Therapeutics 2000 86:201-215) reviews in his "Introduction" on page 202 the daunting task faced by the skilled artisan in developing small molecule regulators of protein-protein interactions, and notes that the process required long periods of trial and error testing before suitable compounds could be developed. Thus the structure of such molecules cannot be readily envisioned by one skilled in the art based upon the guidance provided in the specification.

The specification also does not appear to provide sufficient objective evidence that the claimed method can work *in vivo*. For instance, Applicant's disclosure indicates in Example 2 that cross-linking of the common γ chain antibody is necessary to prevent induction of anergy *in vitro*. However there appears to be insufficient guidance as to how sufficient cross-linking at an appropriate timepoint could be provided *in vivo* to inhibit responsiveness in an anergic T cell. Further, *in vivo* methods utilizing the various "agents" are unpredictable. Examples of the technical difficulties that are encountered include: (1) protein inactivation before producing an effect, i.e. proteolytic degradation, immunological inactivation, or inherently short half-life of the protein; (2) protein failure to reach the target area, i.e. inability to cross the mucosa or absorption by fluids, cells and tissues where the protein has no effect; and (3) unsuitable functional properties, known or unknown, for *in vivo* therapeutic use, i.e. adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Besides the uncertainties associated with pharmaceutical therapies in general for the different "agents", there appears to be insufficient guidance in the specification to direct a person of skill in the art in how to use the agents in a method of inhibiting responsiveness in an anergic T cell *once anergy has been established*. While the specification discloses in Examples 1 and 2 methods for using certain "agents" to prevent the induction of anergy; prevention of the induction of anergy does not provide sufficient objective evidence that anergy can be reversed once established. The ability of different "agents" to reverse established anergy is unpredictable. For instance, Boussiotis et al. (J. Exp. Med. 1993 178:1753-1763, IDS #AI) teach that while IL-2 can prevent the *induction* of anergy in an *in vitro* model system, IL-2 added to the anergized cells does not restore the ability of these T cells to respond when re-challenged with agent (see entire document, especially Figure 7).

Thus given the uncertainties associated with overcoming established anergy, the application *in vivo* of agents to prevent induction of anergy or overcome established anergy, and the use of agents as broadly recited; there appears to be insufficient guidance to direct the skilled artisan in how to use a method for inhibiting responsiveness in an anergic T cell commensurate in scope with the instant claim. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Thus the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Applicant should limit the instant method to the agents set forth in Examples 1 and 2 and indicate a method for preventing induction of anergy *in vitro*, as set forth in those examples in order to obviate this rejection.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 37(c) of this title before the invention thereof by the applicant for patent.

12. Claim 98 is rejected under 35 U.S.C. 102(b) as being anticipated by Beverly et al. (Int. Immunol 1991 4:661-667, IDS #AG; see entire document); as evidenced by Nelson et al. (Nature 1994 369:333-336, IDS #BP; see entire document).

Beverly et al. teach a method for inhibiting responsiveness in an anergic T cell, comprising contacting said T cell with an agent which transduces a signal via the cytokine receptor γ chain such that T cell responsiveness is inhibited (see entire document, especially "Abstract").

IL-2 is an agent which transduces a signal via the cytokine receptor γ chain, as evidenced by the teachings of Nelson et al. (see entire document, especially "Abstract").

As pointed out supra, "inhibiting responsiveness in an anergic T cell" is in effect stimulating a response in said T cells since anergic T cells are unresponsive.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The courts have held that there is no requirement that those of ordinary skill in the art know of the inherent property. See MPEP 2131.01(d) and MPEP 2112 - 2113 for case law on inherency. When a claim recites using an old composition or structure (e.g. IL-2) and the use is directed to a result or *property of that composition* or structure (transducing a signal via the cytokine receptor γ chain), then the claim is anticipated. See MPEP 2112.02. Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

13. Claim 98 is rejected under 35 U.S.C. 102(b) as being anticipated by Boussiotis et al. (J. Exp. Med. 1993 178:1753-1763, IDS #AI; see entire document); as evidenced by Nelson et al. (Nature 1994 369:333-336, IDS #BP; see entire document).

Boussiotis et al. teach a method for inhibiting responsiveness in an anergic T cell, comprising contacting said T cell with an agent which transduces a signal via the cytokine receptor γ chain such that T cell responsiveness is inhibited (see entire document, especially "Figure 6"). In this model of T cell anergy, IL-2 can only inhibit induction of anergy (e.g., Figure 6), not mediate reversal of established anergy (see Figure 7).

IL-2 is an agent which transduces a signal via the cytokine receptor γ chain, as evidenced by the teachings of Nelson et al. (see entire document, especially "Abstract").

As pointed out supra, "inhibiting responsiveness in an anergic T cell" is in effect stimulating a response in said T cells since anergic T cells are unresponsive.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The courts have held that there is no requirement that those of ordinary skill in the art know of the inherent property. See MPEP 2131.01(d) and MPEP 2112 - 2113 for case law on inherency. When a claim recites using an old composition or structure (e.g. IL-2) and the use is directed to a result or *property of that composition* or structure (transducing a signal via the cytokine receptor γ chain), then the claim is anticipated. See MPEP 2112.02. Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

14. Claim 98 is rejected under 35 U.S.C. 102(e) as being anticipated by de Boer et al. (US Pat. No. 5,747,034, see entire document); as evidenced by Nelson et al. (Nature 1994 369:333-336, IDS #BP; see entire document).

de Boer et al. teach a method for inhibiting responsiveness in an anergic T cell, comprising contacting said T cell with an agent which transduces a signal via the cytokine receptor γ chain such that T cell responsiveness is inhibited (see entire document, especially "Example 15" at columns 30-32).

IL-2 is an agent which transduces a signal via the cytokine receptor γ chain, as evidenced by the teachings of Nelson et al. (see entire document, especially "Abstract").

As pointed out supra, "inhibiting responsiveness in an anergic T cell" is in effect stimulating a response in said T cells since anergic T cells are unresponsive.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The courts have held that there is no requirement that those of ordinary skill in the art know of the inherent property. See MPEP 2131.01(d) and MPEP 2112 - 2113 for case law on inherency. When a claim recites using an old composition or structure (e.g. IL-2) and the use is directed to a result or *property of that composition* or structure (transducing a signal via the cytokine receptor γ chain), then the claim is anticipated. See MPEP 2112.02. Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

16. Claim 98 is rejected under 35 U.S.C. 103(a) as being unpatentable over EITHER.
Beverly et al. (Int. Immunol 1991 4:661-667, IDS # AG), OR
Boussiotis et al. (J. Exp. Med. 1993 178:1753-1763, IDS #AI), OR
de Boer et al. (US Pat. No. 5,747,034);
in view of Nelson et al. (Nature 1994 369:333-336, IDS #BP).

The claims are drawn to a method for inhibiting responsiveness in an anergic T cell, comprising contacting said T cell with an agent which transduces a signal via the cytokine receptor γ chain such that T cell responsiveness is inhibited.

Beverly et al., or Boussiotis et al., or de Boer et al. have been discussed supra and teach a method for inhibiting responsiveness in an anergic T cell, comprising contacting said T cell with IL-2 which transduces a signal via the cytokine receptor γ chain such that T cell responsiveness is inhibited.

Beverly et al., or Boussiotis et al., or de Boer et al. do not teach contacting the T cells with IL-4, IL-7 or a cross-linking antibody to the common γ chain.

Nelson et al. have also been discussed supra and teach that IL-2 is an agent which transduces a signal via the cytokine receptor γ chain (see entire document, e.g. "Abstract"). Nelson et al. also teach that the IL-2Rγ chain is a signaling component in the IL-4R and the IL-7R (see especially page 334, last paragraph). Finally, Nelson et al. teach that ligand-induced dimerization is important for signaling (e.g., Figure 1).

Given the teachings of Beverly et al., or Boussiotis et al., or de Boer et al. that IL-2 can prevent the induction of anergy; and the teachings of Nelson et al. that the IL-2Rγ chain is used in signaling not only by the IL-2R, but also by the IL-4R and IL-7R; the ordinary artisan would have been motivated to utilize these alternate cytokines or an antibody to the common γ chain in a method of inhibiting responsiveness in an anergic T cell. Given the teachings of Nelson et al. that all three cytokines signal via a common γ chain, it would have been obvious to the ordinary artisan at the time the invention was made to substitute either one cytokine for the other in a method of inhibiting responsiveness in an anergic T cell, or to directly target the common γ chain with an antibody. Given the teachings of Nelson that ligand-induced dimerization is important, the ordinary artisan would have selected an antibody to the common g chain which cross-links (or could be cross-linked with an secondary agent) in order to provide dimerization-mediated signaling. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. As stated supra, the language of instant claim 98 of "inhibiting responsiveness in an anergic T cell" is considered to be stimulating a response in said T cells since anergic T cells are unresponsive. It is noted that pending claim 98 of USSN 08/270,152 recites "stimulating responsiveness in an anergic T cell" wherein the agent is an antibody to the common γ chain. Because there is some uncertainty with respect to the language of claim 98 of USSN 08/270,152, as well as instant claim 98; *Applicant is requested to confirm that these claims do not represent overlapping subject matter with regards to the end effect on the anergic T cell.*

If Applicant indicates that the subject matter of claim 98 of USSN 08/270,152 and instant claim 98 have overlapping subject matter, **THEN** the following provisional double patenting rejection would apply.

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claim 98 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 98 of copending Application No. 08/270,152. Although the conflicting claims are not identical, they are not patentably distinct from each other because IF the method recited in each claim results in the same effect in the T cell; THEN the species of agent recited in claim 98 of 08/270,152 would render the genus recited in 08/556,038 obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
April 16, 2001

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
4/17/01